Original Article

Developing The Harmonized CTD Module 3 Data For Australia And South Africa Markets With Europe For A Generic Drug Product Approval

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Abstract

Introduction: The drive for improved regulatory systems and the establishment of a more effective regulatory framework in Australia (AU) and South Africa (ZA) has been evident for the past two decades. Navigating through South African Health Product Regulatory Authority (SAHPRA) and Therapeutic Goods Administration Australia (TGA) requirements poses a challenge for generic product manufacturers while approaching market authorizations.

Objective: The present work was an attempt to understand the Australia (AU) and South Africa (ZA) specific additional data requirement of Chemistry, Manufacturing and Control (CMC) in order to build Module 3 dossier and ensuring timely approval of generic product in ZA and AU market.

Methodology: This research work was a mix of Applied, Conceptual and Empirical research types.

Results: With the adoption of a large number of EU regulations, it is easier to use most of the data generated for the EU market. However, there is still extensive AU and ZA specific CMC requirements, as discussed and presented in this article, which must be considered at the development and global dossier preparation stages to ensure swift and timely approval in AU and ZA.

Conclusion: It is imperative to identify, generate and present this additional data for AU and ZA, during global generic product regulatory filing to save cost and timely approval of the generic products in ZA and AU. It is recommended to keep abreast with ever-changing regulations in ZA and AU.

Keywords: Australia, South Africa, Module 3, Global Dossier, CMC

INTRODUCTION

The highly complex regulatory environment, varied approval timelines, and specific data requirements, including costly and time taking Chemistry, Manufacturing, Control data between countries, have been an issue for the industry to ensure an uninterrupted supply of high-quality, safe and effective medicines around of the world. The data developed for a country may not apply to other countries, leading to many different data generation and compilation by regulatory professionals.

Australia is considered a potential market for generic products. With time, there has been tremendous growth in the size of the Australian generics market. During the last decade, Australia health regulatory agency i.e., Therapeutic Goods Administration (TGA), has made significant changes in regulations for the benefit of industry, regulators, and patients, thereby establishing Australia regulations be of global standards with transparency, straightforward process and timelines. However, there are still many Australia-specific requirements that are unique compared to other leading regulated markets[1].

In South Africa, before June 2011, PART format was the format for submission of a dossier for drug product approval in South Africa (ZA) via Medicines Control Council (MCC). In June 2011, ZA CTD format was implemented for this purpose. Though it was an important step towards globalization of South African regulations, however there are differences in ZA CTD when compared to ICH CTD. In today's world, the global dossier is vital for cost savings and timely approvals; understanding the difference between CTD structure and its requirement is essential. Further, some

specific requirements for quality sections require specific data generation for South Africa during product development for ease of timely approval and submission along with global markets. The South African Healthcare Products Regulatory Authority (SAHPRA), which has taken the role of Medicine Control Council (MCC) as an independent entity that reports to the National Minister of Health through its Board, has taken many steps to harmonize with EU[2-6].

Both SAHPRA and TGA recognized approval given for a product by a regulated market health agency and qualified such product and rely on evaluation report of these reference countries, leading to early approval. In South Africa, SAHPRA recognized many regulatory authorities and procedures to qualify for a reliance evaluation pathway. These regulatory authorities are called Recognized Regulatory Authorities (RRA) [7, 8]. A list of South Africa RRA is provided in Table 1. In Australia, the Comparable Overseas Regulators (COR) report-based process is to reduce duplication of evaluation of prescription medicines that a COR has already approved. This also helps in shortened evaluation and decision timeframe[9]. The countries and jurisdictions part of CORs is presented Table 2. By understanding the requirements of such a procedure, data development efforts and time for approval can both be saved.

Therefore, the present work was an attempt to understand the Australia (AU) and South Africa (ZA) specific additional data requirement of Chemistry, Manufacturing and Control (CMC) in order to build Module 3 dossier and ensuring timely approval of generic product in ZA and AU market.

METHODOLOGY

This research work is a mix of Applied, Conceptual and Empirical research types. The information to create a regulatory strategy for product development and regulatory submissions was obtained from all possible publications, including draft guidelines, Reflection papers and Concept papers. ICH[10] and other adopted guidelines in various regions, i.e., United States Food and Drug Administration (USFDA), European Medical Agency (EMA) [11], Therapeutic Goods Administration (TGA) Australia[12-18], South African Healthcare Products Regulatory Authority (SAHPRA) [19-21].

RESULTS AND DISCUSSION

Module 3.2.P.1 Description and Composition of Drug Product

For South Africa:

- If the applicant is using excipient of one grade, there is a need in South Africa to submit a statement for differentiation between grades.
- Pharmacopeial reference of European Pharmacopoeia (Ph. Eur.) is preferable in the EU, however for South Africa, both Ph. Eur. And United States Pharmacopoeia (USP) is acceptable[21].

For Australia:

- All proprietary and non-proprietary ingredients must be listed as Australian Approved Names (AANs)[13]. AAN should be presented in 3.2.P.1 section. For example: In EU monograph, the name is 'Perindopril tert-butylamine Ph. Eur.' however AAN for the same ingedient is 'Perindopril erbumine'.
- If colourings used in proposed topical or oral medications are not in the published ARTG list, the applicant should provide data to the TGA for evaluation and approval before submitting of finished product dossier[15].
- For Global Dossier, please check US FDA inactive ingredient guide (IIG) limits during generic product development.

Module 3.2.P.2 Pharmaceutical Development

For South Africa:

- For EU, it is mandatory to use EU innovator products for development studies and Bioequivalence studies however, for ZA, local or foreign innovators, both are acceptable[20].
- For ZA, multimedia dissolution data needs to be generated at Good Manufacturing Practice (GMP) approved site.
- Bridging data between innovator products and generic products in the EU is provided in Module 3.2.P.2 however, in ZA, it is part of Module 3.2.R.1[19].

For Australia:

- Developmental data can be generated against any other region's innovator.
- Bioequivalence study is mandatory with AU innovator product.
- If tablets are scored, information must be provided to demonstrate that the splitting was done correctly and that the sections complied with pharmacopoeial standards for uniformity of weight/content[16].
- Research into how ethanol affects in vitro disintegration and release is required for dose formulations with modulated release[16, 22].

Module Section 3.2.P.3 Manufacture

For South Africa:

- The detailed packaging process is mandatory to be provided in this section; however it is not mandatory for the EU.
- Hold time studies is not mandatory in ZA however, it is mandatory for the EU.

Module 3.2.P.4 Control of Excipients

- For South Africa, unlike the EU, identification of the Inactive Pharmaceutical Ingredient (IPI) should be performed irrespective of the availability of a Certificate of Analysis (CoA) from the supplier.
- For Australia, all proprietary and non-proprietary ingredients must be listed as Australian Approved Names (AANs). AAN should be presented in 3.2.P.4.1 section.

Module 3.2.P.5 Control of Drug Product

For South Africa:

- A separate stability specification is required to be provided in addition to the release and shelf-life specifications in contrast to EU
- For South Africa, batch analysis reports for two batches are sufficient; however EU requirement is for three batches.

For Australia:

- All medicines should comply with the Therapeutic Goods Order No.100: Microbiological Standards for Medicines[17].
- Tablets and capsules should comply with the requirements of the TGO 78 : General Standard for Tablets and Capsules.
- Assay shelf life recommended limit is 92.5 – 107.5 % however, in the EU, it is 95-105%.
- It is recommended to follow the finished dosage form monograph of USP, if available.
- For generic medicine applications, limits above the ICH threshold may need to be qualified against Australian reference products near or past expiry date.

Module 3.2.P.7 Container Closure System

For South Africa:

- Unlike EU, South Africa requires a vendor's certificate of analysis for all packaging materials.

For Australia:

- Applicants must follow Therapeutic Goods Order (TGO) guidance for Child-resistant packaging requirements for medicines[14].

Section 3.2.P.8 Stability Data

For South Africa:

- As per EU requirements, the stability protocol of exhibit batches to be included in the dossier however, it is not mandatory for South Africa.
- For a generic application, the current SAHPRA stability standard mandates a minimum of six months of long-term stability data and three months of accelerated stability data. To enable extended retest periods, SAHPRA would like that twelve months' long-term (and six months accelerated) stability data be included in the revised registration application[16].

For Australia:

- For multi-dose products, the following must be provided:
  - Information on antimicrobial preservative efficacy data at the beginning and end of the closed shelf life, as specified in TGO 100 Microbiological Standards for Medicines[17].
  - Information on microbiological challenge testing/simulated use testing as applicable to support the open shelf life (in-use) period.
- In the case of chemical entities, no less than six months of real-time and accelerated stability data must be provided[12].
- For non-conventional, including modified release dosage forms, no less than 12 months real-time and 6 month accelerated stability data must be provided[12].

There is a significant difference between South Africa and EU section 3.2.R Regional information as a lot of CMC data on drug products in South Africa goes to Module 3.2.R[18], whereas in EU, all CMC data on drug products get presented in Module 3.2.P only. Below sections cover the key differences in 3.2.R. section of detailed differences between ZA CTD and EU:

Module 3.2.R.1

- In EU, section 3.2.R.1 provides Process Validation Protocol and Scheme for commercial batches however, in ZA this section provides information on Pharmaceutical and Biological Availability. It contains research done on exhibit and clinical batches. The data includes dissolution studies, data, reports, certificates of analysis for innovator drugs, clinical batches of generic products, and information about reference products (both domestic and international). This section also includes comparative dissolution data, which is crucial for the clearance of generic products in South Africa where the requirements are stricter.

Module 3.2.R.2

- In the EU, provide information on Medical Devices; however, in ZA, this section includes details on the Parent API manufacturer, who may have multiple API manufacturing facilities.

Module 3.2.R.3

- In EU and ZA, both provide information on Certificate(s) of Suitability (CEPs).

Module 3.2.R.4

- In EU, section 3.2.R.4 provides information on Materials of animal and/or human origin; however, in SA, if the same API is acquired from different manufacturers, information on those producers is provided in this section. The applicant must submit a comparative study report on API manufacturers, comparative findings, confirmation of conformity with regulations, and certificates of analysis from each API supplier.

Table 1: List of South Africa's Recognized Regulatory Authorities (RRA)

Country/ Region	Regulatory Authority
Europe	European Medicines Agency Centralised Procedure (EMA CP)
Europe	European Medicines Agency Decentralised Procedure (EMA DCP)
Canada	Health Canada
United Kingdom	Medicines and Healthcare products Regulatory Agency (MHRA)
Japan	Ministry of Health, Labour and Welfare (MHLW)
Switzerland	Swiss Agency for Therapeutic Products (Swissmedic)
Australia	Therapeutic Goods Administration (TGA),
United States	Food and Drug Administration (FDA)
Additional procedures	
World Health Organisation Prequalification (WHO PQ)	
Zazibona collaborative procedure	

Table 2: List of Countries and Jurisdictions part of Australia's Comparable Overseas Regulators (COR) report-based process

Country	Regulatory Authority
Canada	Health Canada
Japan	Pharmaceuticals and Medical Devices Agency (PMDA)
Singapore	Health Science Authority Singapore (HSA)
Switzerland	Swiss Medic
United Kingdom	Medicines and Healthcare products Regulatory Agency (MHRA)
United States	Food and Drug Administration (FDA)
Jurisdictions	
European Union	European Medicines Agency (EMA) - centralised and decentralised processes

CONCLUSION

Over the decade of great work to make regulations streamline and in best practices of global standards, TGA has become one of the most efficient and regulated regulatory agencies. As studied and presented in this paper, the timelines are apparent, strict and transparent, which helps both the applicant and the health agency. With the adoption of many EU regulations, it is easier to use most of the data generated for the EU market. However, there is still Australia specific CMC and dossier requirement, as discussed and presented in this article, which must be considered at the development and global dossier preparation stages to ensure swift and timely approval in Australia.

In the last one decade, South Africa's regulations have taken a significant leap to make its regulations in line with global regulations standards. SAHPRA is undoubtedly moving towards a highly regulated market. With the creation & implementation of ZA CTD and harmonization with many EU guidance, it is now comparatively easier and quicker to develop data and obtain approval in the South Africa market in parallel to other regulated markets. However, at the same time, it is crucial to understand that the ZA CTD structure still has some differences from ICH CTD, as presented in this article. Further many critical requirements are only specific to the South Arica. It is vital to identify and generate this additional data for the South Africa during global generic product development to save cost and timely approval of the generic products in the South Africa. It is recommended to keep abreast with ever-changing regulations in South Africa.

DECLARATION

Conflict of interest: No conflict of interest in the manuscript.

Author's contribution: Author VT was involved in data collection, data analysis, and manuscript writing. Author PJ was involved in the conceptualization, data validation, and critical review of the manuscript.

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